Cartilage Regeneration by the Chondrogenic Small Molecule PRO1 during Osteoarthritis

Grant Award Details

Cartilage Regeneration by the Chondrogenic Small Molecule PRO1 during Osteoarthritis

Grant Type: Early Translational II

Grant Number: TR2-01829

Project Objective: Identify and elect best small molecule derived from POR to induces chondrogenesis by changing the course of differentiation of MSC to chondrocytes to be develop for Osteoarthritis (OA).

Investigator:

Name:	Peter Schultz
Institution:	Scripps Research Institute
Type:	PI

Disease Focus: Arthritis, Bone or Cartilage Disease

Human Stem Cell Use: Adult Stem Cell

Cell Line Generation: Other

Award Value: $6,047,249

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE Year 4

View Report

Grant Application Details

Application Title: Cartilage Regeneration by the Chondrogenic Small Molecule PRO1 during Osteoarthritis

Public Abstract:

The ability to direct the differentiation of resident mesenchymal stem cells (MSCs) towards the cartilage lineage offers considerable promise for the regeneration of articular cartilage after traumatic joint injury or age-related osteoarthritis (OA). MSCs can be stimulated in vitro to form new functional cartilage. In the OA-affected joint, the repair is insufficient, leaving a damaged matrix, suggesting that key factors are missing to properly direct the regenerative process. Molecules that activate the chondrogenic potential of cartilage stem cells may potentially prevent further cartilage destruction and stimulate repair of cartilage lesions.

Currently there are no disease-modifying therapeutics available for the 40 million Americans suffering from OA. Therapeutic options are limited to oral and intra-articularly injected pain medications and joint replacement surgery. The primary objective of this project is to develop a non-invasive, therapeutic for the regeneration of cartilage in OA. This new therapy will target the resident MSCs in the joint, stimulate production of new cartilage matrix, promote repair and thus limit additional joint damage and improve joint pain and function.

To provide a proof-of-concept for our strategy, a cell-based screen of a diverse small molecule library led to compounds capable of enhancing the formation of articular cartilage (chondrogenesis) from MSCs in vitro. In secondary assays, molecules were assessed for protection of the existing cartilage against induced tissue damage. Through these approaches, the lead low molecular weight small molecule PRO1 was identified which promotes cartilage differentiation and protects cartilage from damage. PRO1 reproducibly demonstrated in vivo efficacy in two animal models of OA (surgical and enzyme-induced). OA-associated pain was reduced and the architecture of the cartilage was restored. PRO1 therefore appears to activate the regenerative potential of the resident cartilage stem cells.

Statement of Benefit to California:

Osteoarthritis (OA) is the most prevalent musculoskeletal disease and globally the 4th leading cause of Years Lost to Disease (YLD). OA affects over 40 million Americans and the magnitude of the problem is predicted to increase even further with the obesity epidemic and aging of the baby boomer generation. It is estimated that 80% of the population will have radiographic evidence of OA by age 65 years. The annual economic impact of arthritis in the U.S. is estimated at over $100 billion, representing more than 2% of the gross domestic product. OA accounts for 25% of visits to primary care physicians. In 2004 OA patients received 650,000 knee and hip replacements at a cost of $26 billion. Without change in treatment options 1.8 million joint replacements will be performed in 2015.

OA is a painful, degenerative type of arthritis; physical activity can become difficult or impossible. Some patients with osteoarthritis are forced to stop working because their condition becomes so limiting. OA can interfere with a patient's ability to even perform routine daily activities, resulting in a decrease in quality of life. The goals of osteoarthritis treatment are to relieve pain and other symptoms, preserve or improve joint function, and reduce physical disability. Current therapeutic options are limited to pain medications and joint replacement for patients with advanced disease. No disease-modifying OA drugs are approved for clinical use. OA is thus a major unmet medical need with a huge clinical and socioeconomic impact and a complete absence of effective therapies. Clearly the development of a new therapeutic that is both symptom and disease modifying would have a significant impact on the well-being of Californians and reduce the negative economic impact on the state resulting from this highly prevalent disease.

Source URL: https://www.cirm.ca.gov/our-progress/awards/cartilage-regeneration-chondrogenic-small-molecule-pro1-during-osteoarthritis